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NEWS 14 Nov 25 More calculated properties added to REGISTRY  
NEWS 15 Dec 04 CSA files on STN  
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ENERGY, INSPEC  
NEWS 20 Feb 13 CANCERLIT is no longer being updated  
NEWS 21 Feb 24 METADEX enhancements  
NEWS 22 Feb 24 PCTGEN now available on STN  
NEWS 23 Feb 24 TEMA now available on STN  
NEWS 24 Feb 26 NTIS now allows simultaneous left and right truncation  
NEWS 25 Feb 26 PCTFULL now contains images  
NEWS 26 Mar 04 SDI PACKAGE for monthly delivery of multifile SDI results  
NEWS 27 Mar 19 APOLLIT offering free connect time in April 2003  
NEWS 28 Mar 20 EVENTLINE will be removed from STN  
NEWS 29 Mar 24 PATDPAFULL now available on STN  
NEWS 30 Mar 24 Additional information for trade-named substances without  
structures available in REGISTRY  
NEWS 31 Apr 11 Display formats in DGENE enhanced  
NEWS 32 Apr 14 MEDLINE Reload  
NEWS 33 Apr 17 Polymer searching in REGISTRY enhanced  
NEWS 34 Apr 21 Indexing from 1947 to 1956 being added to records in CA/CAPLUS  
NEWS 35 Apr 21 New current-awareness alert (SDI) frequency in  
WPIDS/WPINDEX/WPIX  
  
NEWS EXPRESS April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT  
MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),  
AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003

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FILE 'HOME' ENTERED AT 16:36:11 ON 24 APR 2003

=> fil reg		
COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	0.21	0.21

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STRUCTURE FILE UPDATES: 23 APR 2003 HIGHEST RN 504385-01-7  
DICTIONARY FILE UPDATES: 23 APR 2003 HIGHEST RN 504385-01-7

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

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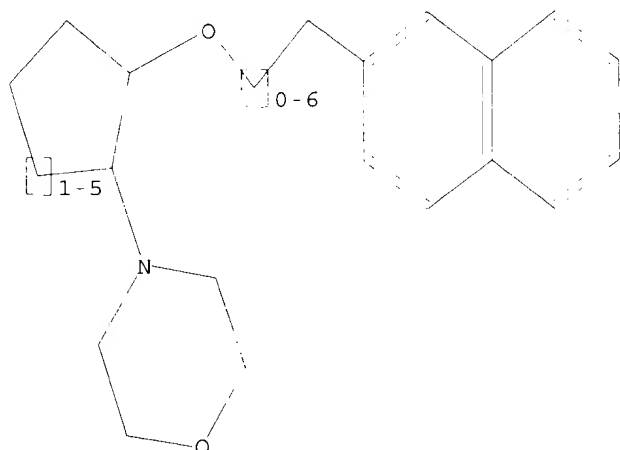
Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:  
<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

=>  
Uploading 09913373.str

L1 STRUCTURE UPLOADED

=> d  
L1 HAS NO ANSWERS  
L1 STR

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Structure attributes must be viewed using STN Express query preparation.

```
=> s l1 sss sam
SAMPLE SEARCH INITIATED 16:36:53 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -      23 TO ITERATE
```

```
100.0% PROCESSED      23 ITERATIONS      1 ANSWERS
SEARCH TIME: 00.00.01
```

```
FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:   173 TO   747
PROJECTED ANSWERS:      1 TO    80
```

```
L2      1 SEA SSS SAM L1
```

```
=> s l1 full
FULL SEARCH INITIATED 16:36:57 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -      528 TO ITERATE
```

```
100.0% PROCESSED      528 ITERATIONS      8 ANSWERS
SEARCH TIME: 00.00.01
```

```
L3      8 SEA SSS FUL L1
```

```
=> fil caplus
COST IN U.S. DOLLARS      SINCE FILE      TOTAL
                           ENTRY      SESSION
FULL ESTIMATED COST      148.15      148.36
```

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FILE COVERS 1907 - 24 Apr 2003 VOL 138 ISS 17  
FILE LAST UPDATED: 23 Apr 2003 (20030423/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l3 full  
L4 5 L3

=> d l4 1-5 ibib abs histr  
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The following are valid formats:

ABS ----- GI and AB  
ALL ----- BIB, AB, IND, RE  
APPS ----- AI, PRAI  
BIB ----- AN, plus Bibliographic Data and PI table (default)  
CAN ----- List of CA abstract numbers without answer numbers  
CBIB ----- AN, plus Compressed Bibliographic Data  
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DMAX ----- MAX, delimited for post-processing  
FAM ----- AN, PI and PRAI in table, plus Patent Family data  
FBIB ----- AN, BIB, plus Patent FAM  
IND ----- Indexing data  
IPC ----- International Patent Classifications  
MAX ----- ALL, plus Patent FAM, RE  
PATS ----- PI, SO  
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SCAN ----- CC, SX, TI, ST, IT (random display, no answer numbers;  
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IALL ----- ALL, indented with text labels  
IBIB ----- BIB, indented with text labels  
IMAX ----- MAX, indented with text labels  
ISTD ----- STD, indented with text labels  
  
OBIB ----- AN, plus Bibliographic Data (original)  
OIBIB ----- OBIB, indented with text labels  
  
SBIB ----- BIB, no citations  
SIBIB ----- IBIB, no citations  
  
HIT ----- Fields containing hit terms  
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containing hit terms  
HITRN ----- HIT RN and its text modification  
HITSTR ----- HIT RN, its text modification, its CA index name, and

its structure diagram  
 HITSEQ ----- HIT RN, its text modification, its CA index name, its  
 structure diagram, plus NTE and SEQ fields  
 FHITSTR ----- First HIT RN, its text modification, its CA index name, and  
 its structure diagram  
 FHITSEQ ----- First HIT RN, its text modification, its CA index name, its  
 structure diagram, plus NTE and SEQ fields  
 KWIC ----- Hit term plus 20 words on either side  
 OCC ----- Number of occurrence of hit term and field in which it occurs

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 ENTER DISPLAY FORMAT (BIB):all

L4 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2003 ACS  
 AN 2001:591832 CAPLUS  
 DN 136:63572  
 TI pH-dependent blocking actions of three novel antiarrhythmic compounds on K<sup>+</sup> and Na<sup>+</sup> currents in rat ventricular myocytes  
 AU Franciosi, S.; McLarnon, J. G.  
 CS Department of Pharmacology and Therapeutics, University of British Columbia, Faculty of Medicine, Vancouver, BC, V6T 1Z3, Can.  
 SO European Journal of Pharmacology (2001), 425(2), 95-107  
 CODEN: EJPHAZ; ISSN: 0014-2999  
 PB Elsevier Science B.V.  
 DT Journal  
 LA English  
 CC 1-3 (Pharmacology)  
 AB Three novel chem. related compds. were studied for their pH-dependent ion channel blocking actions on the transient outward K<sup>+</sup> current (I<sub>to</sub>) and the Na<sup>+</sup> current (I<sub>Na</sub>) in isolated rat ventricular myocytes. The (.+.-)-trans-naphthylethoxycyclohexylamines, RSD1108, RSD1070 and RSD1067, showed similar potencies in reducing the inactivation time course of I<sub>to</sub> at pH 7.4. However, RSD1108 (pK<sub>a</sub> 6.8) was a more potent blocker of I<sub>to</sub> at pH 6.4 than the other two compds. (pK<sub>a</sub> values near 8.0). The redn. of inactivation times induced by the RSD compds. was consistent with open channel blockade and in consequence an open channel block model was used in order to est. blocking and unblocking rate consts. This anal. showed no apparent correlation between pK<sub>a</sub> and onward blocking rate consts. for the compds. However, the unblocking rate const. for the low pK<sub>a</sub> compd. RSD1108 at acid pH decreased markedly from that found at normal pH. Both RSD1108 and RSD1070 showed an enhanced potency to block I<sub>Na</sub> at acid pH relative to pH 7.4. However, RSD1108 showed significantly less inhibition of I<sub>Na</sub> at both pH values compared to RSD1070 and RSD1067. Differences in channel block were also evident between RSD1070 and RSD1067, which could be attributed to the difference in naphthyl groups between their chem. structures. The compds. exhibited use- and frequency-dependent blockade of I<sub>Na</sub> with the amt. of use-dependent blockade greater for RSD1108 and RSD1067 than for RSD1070 at acid pH compared to neutral pH. Greater frequency-dependent inhibition was apparent for RSD1108 as compared to RSD1070 and RSD1067 at both pH 7.4 and 6.4. These results point out the

- importance of the magnitude of pKa and chem. structure in ion channel blocking actions of a series of structurally related compds.
- ST naphthylethoxycyclohexylamine structure antiarrhythmic pH ion channel blocker
- IT Heart, disease  
(ischemia; pH-dependent blocking actions of novel antiarrhythmic compds. on K<sup>+</sup> and Na<sup>+</sup> currents in rat ventricular myocytes)
- IT Antiarrhythmics  
(pH-dependent blocking actions of novel antiarrhythmic compds. on K<sup>+</sup> and Na<sup>+</sup> currents in rat ventricular myocytes)
- IT Structure-activity relationship  
(potassium channel-blocking; pH-dependent blocking actions of novel antiarrhythmic compds. on K<sup>+</sup> and Na<sup>+</sup> currents in rat ventricular myocytes)
- IT Ion channel blockers  
(potassium; pH-dependent blocking actions of novel antiarrhythmic compds. on K<sup>+</sup> and Na<sup>+</sup> currents in rat ventricular myocytes)
- IT Structure-activity relationship  
(sodium channel-blocking; pH-dependent blocking actions of novel antiarrhythmic compds. on K<sup>+</sup> and Na<sup>+</sup> currents in rat ventricular myocytes)
- IT Ion channel blockers  
(sodium; pH-dependent blocking actions of novel antiarrhythmic compds. on K<sup>+</sup> and Na<sup>+</sup> currents in rat ventricular myocytes)
- IT Heart  
(ventricle, myocyte; pH-dependent blocking actions of novel antiarrhythmic compds. on K<sup>+</sup> and Na<sup>+</sup> currents in rat ventricular myocytes)
- IT 12408-02-5, Hydrogen ion, biological studies  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(gradient; pH-dependent blocking actions of novel antiarrhythmic compds. on K<sup>+</sup> and Na<sup>+</sup> currents in rat ventricular myocytes)
- IT 244762-60-5, RSD 1067 244762-62-7, RSD1070 244762-87-6, RSD 1108  
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PRP (Properties); BIOL (Biological study)  
(pH-dependent blocking actions of novel antiarrhythmic compds. on K<sup>+</sup> and Na<sup>+</sup> currents in rat ventricular myocytes)
- IT 17341-25-2, Sodium ion, biological studies 24203-36-9, Potassium ion, biological studies  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(pH-dependent blocking actions of novel antiarrhythmic compds. on K<sup>+</sup> and Na<sup>+</sup> currents in rat ventricular myocytes)

RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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(26) Yong, S; J Pharmacol Exp Ther 1999, V289, P236 CAPLUS

L4 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2003 ACS

AN 2000:573767 CAPLUS

DN 133:176973

TI Cycloalkyl amine compounds and their use as antiarrhythmics and sodium channel blockers

IN Beatch, Gregory N.; Plouvier, Bertrand M. C.; Walker, Michael J. A.; Wall, Richard A.; Zolotoy, Alexander B.

PA Nortran Pharmaceuticals Inc., Can.

SO PCT Int. Appl., 59 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM C07C217-00

CC 24-4 (Alicyclic Compounds)

Section cross-reference(s): 1, 27, 28

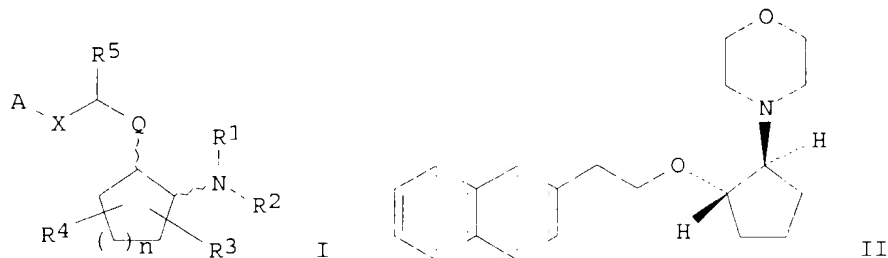
FAN.CNT 1

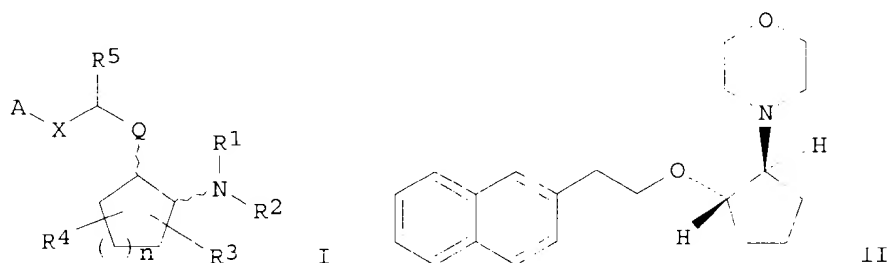
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000047547	A2	20000817	WO 2000-CA117	20000210
	WO 2000047547	A3	20001214		
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, PU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				

PRAI US 1999-119887P P 19990212

OS MARPAT 133:176973

GI





- AB Aminocycloalkyl compds. I are disclosed [wherein n = 1, 3, 4; Q = O or OCO; X = bond, (un)substituted CH<sub>2</sub>Y, (un)substituted CH:CH; Y = bond, O, S, alkylene; R<sub>1</sub>, R<sub>2</sub> = H, alkyl, alkoxyalkyl, hydroxyalkyl, aralkyl; or NR<sub>1</sub>R<sub>2</sub> may form a variety of mono- or bicyclic ring systems; R<sub>3</sub>, R<sub>4</sub> = H, OH, alkyl, alkoxy; or R<sub>3</sub>R<sub>4</sub> may form a spiro ring with 5 or 6 members and 1 or 2 atoms of O and/or S; R<sub>5</sub> = H, alkyl, aryl, benzyl; A = alkyl, carbocyclyl, or (un)substituted Ph, naphthyl, indenyl, indolyl, acenaphthenyl, or fluorenyl]. The compds. may be incorporated in compns. and kits. The invention also discloses a wide variety of in vitro and in vivo uses for the compds. and compns., including the treatment of arrhythmia and the prodn. of local analgesia and anesthesia. Two examples were prepd. as HCl salts, and their free bases and their salts and solvates are claimed. For instance, (1R,2R)/(1S,2S)-II.HCl (III) was prepd. by a sequence of: (1) reaction of morpholine with cyclopentene oxide; (2) mesylation of the resulting alc.; (3) etherification of the mesylate with 2-naphthaleneethanol; and (4) acidification with ethereal HCl. In a test for efficacy against cardiac arrhythmias in rats (induced by coronary artery occlusion), III had an ED<sub>50</sub> of 1.5 .mu.M/kg/min i.v.
- ST cycloalkylamine prepn antiarrhythmic sodium channel blocker; morpholinyl naphthaleneethoxy cyclopentane prepn antiarrhythmic; ketopyrrolidinyl dichlorophenethoxy cyclopentane prepn antiarrhythmic
- IT Muscular dystrophy  
(Becker's, treatment; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)
- IT Sexual behavior  
(aphrodisiacs for; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)
- IT Mental disorder  
(dementia, treatment; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)
- IT Digestive tract  
Respiratory tract  
(disease, treatment; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)
- IT Heart, disease  
(failure, treatment; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)
- IT Paralysis  
(hyperkalemic periodic, treatment; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)
- IT Bladder  
(incontinence, treatment; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)
- IT Intestine, disease  
(irritable bowel syndrome, treatment; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)

09913373

- IT Brain, disease
- Heart, disease
  - (ischemia, treatment; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)
- IT Anesthetics
  - (local; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)
- IT Heart, disease
  - (long QT syndrome, treatment; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)
- IT Fever and Hyperthermia
  - (malignant, treatment; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)
- IT Muscle, disease
  - (paramyotonia congenita, treatment; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)
- IT Allergy inhibitors
- Analgesics
- Anti-Alzheimer's agents
- Anti-inflammatory agents
- Antiarrhythmics
- Antiarthritics
- Antiasthmatics
- Anticonvulsants
- Antidepressants
- Antidiabetic agents
- Antihypertensives
- Antihypotensives
- Antimigraine agents
- Antiparkinsonian agents
- Antipsychotics
- Antitussives
- Anxiolytics
- Cardiovascular agents
- Immunosuppressants
- Ion channel blockers
- Nervous system agents
  - (prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)
- IT Ion channel blockers
  - (sodium; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)
- IT Brain, disease
  - (stroke, treatment; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)
- IT Alopecia
- Autoimmune disease
- Cystic fibrosis
- Eye, disease
- Muscle, disease
- Myasthenia gravis
- Transplant rejection
  - (treatment; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)
- IT **288394-73-0P**, (1R,2R)/(1S,2S)-2-(4-Morpholinyl)-1-(2-naphthaleneethoxy)cyclopentane monohydrochloride 288394-74-1P,  
(1R,2R)/(1S,2S)-2-(3-Ketopyrrolidin-1-yl)-1-(2,6-dichlorophenoxy)cyclopentane monohydrochloride **288394-75-2P**,  
(1R,2R)/(1S,2S)-2-(4-Morpholinyl)-1-(2-naphthaleneethoxy)cyclopentane

288394-76-3P, (1R,2R)/(1S,2S)-2-(3-Ketopyrrolidinyl)-1-(2,6-dichlorophenethoxy)cyclopentane  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)

IT 176-33-0P, 1,4-Dioxa-7-azaspiro[4.4]nonane 95656-88-5P, N-Benzyloxycarbonyl-3-pyrrolidinol 109433-72-9P, (1R,2R)/(1S,2S)-2-(4-Morpholinyl)cyclopentanol 130312-02-6P, N-Benzyloxycarbonyl-3-pyrrolidinone 139524-57-5P, 7-Benzyloxycarbonyl-1,4-dioxa-7-azaspiro[4.4]nonane 288394-77-4P, (1R,2R)/(1S,2S)-2-(4-Morpholinyl)cyclopentyl mesylate 288394-78-5P, (1R,2R)/(1S,2S)-2-(1,4-Dioxa-7-azaspiro[4.4]non-7-yl)cyclopentanol 288394-79-6P, (1R,2R)/(1S,2S)-2-(1,4-Dioxa-7-azaspiro[4.4]non-7-yl)-1-(2,6-dichlorophenethoxy)cyclopentane  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(intermediate; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)

IT 110-91-8, Morpholine, reactions 285-67-6, Cyclopentene oxide 501-53-1, Benzyl chloroformate 1485-07-0, 2-Naphthaleneethanol 2799-21-5 30595-79-0, 2,6-Dichlorophenethanol  
 RL: RCT (Reactant); RACT (Reactant or reagent)

(starting material; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)

L4 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2003 ACS

AN 1999:640819 CAPLUS

DN 131:257571

TI Preparation of aralkyl morpholinocyclohexyl ethers and analogs as antiarrhythmic agents

IN Bain, Allen I.; Beatch, Gregory N.; Longley, Cindy J.; Plouvier, Bertrand M. C.; Sheng, Tao; Walker, Michael J. A.; Wall, Richard A.; Yong, Sandro L.; Zhu, Jiqun; Zolotoy, Alexander B.

PA Nortran Pharmaceuticals Inc., Can.

SO PCT Int. Appl., 141 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM C07C217-52

ICS C07D295-096; C07D207-04; C07D333-56; C07D207-24; C07D295-185; C07D277-04; A61K031-13; A61K031-40; A61K031-41; A61K031-535

CC 28-13 (Heterocyclic Compounds (More Than One Hetero Atom))

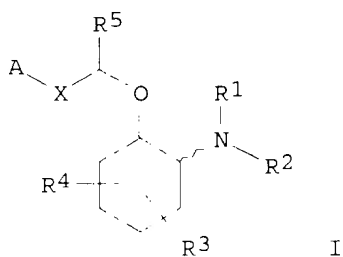
Section cross-reference(s): 1

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9950225	A1	19991007	WO 1999-CA280	19990401
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2326777	AA	19991007	CA 1999-2326777	19990401

09913373

AU 9930215	A1	19991018	AU 1999-30215	19990401
AU 751772	B2	20020829		
EP 1087934	A1	20010404	EP 1999-911550	19990401
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, LT, LV, FI				
BR 9909282	A	20011016	BR 1999-9282	19990401
EE 200000583	A	20020215	EE 2000-200000583	19990401
JP 2002509908	T2	20020402	JP 2000-541135	19990401
NO 2000004897	A	20001113	NO 2000-4897	20000929
PRAI US 1998-80347P	P	19980401		
US 1999-118954P	P	19990205		
WO 1999-CA280	W	19990401		
OS MARPAT 131:257571				
GI				



AB RZCHR5OZ1NR1R2 [R = (cyclo)alkyl, (un)substituted Ph, naphthyl, etc.; R1,R2 = H, (ar)alkyl, alkoxyalkyl, hydroxyalkyl; NR1R2 = heterocyclyl; R5 = H, alkyl, CH2Ph, aryl; Z = bond, (un)substituted alkylene, -CH2O, -CH:CH, etc.; Z1 = (un)substituted 1,2-cyclohexylene] were prepd. as cardiac Na channel blockers. Thus, cyclohexene oxide was aminated by morpholine and the O-mesylated product etherified by 2-naphthaleneethanol to give title compd. trans-I.

ST aralkyl morpholinocyclohexyl ether prepn antiarrhythmic agent

IT Antiarrhythmics

(morpholinocyclohexyl ethers and analogs)

IT Analgesics

(prepn. of aralkyl morpholinocyclohexyl ethers and analogs as antiarrhythmic agents)

IT Ion channel blockers

(sodium; prepn. of aralkyl morpholinocyclohexyl ethers and analogs as antiarrhythmic agents)

IT 244763-31-3P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BYP (Byproduct); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(prepn. of aralkyl morpholinocyclohexyl ethers and analogs as antiarrhythmic agents)

IT	<b>244762-60-5P</b>	<b>244762-61-6P</b>	244762-62-7P	244762-63-8P	
	244762-64-9P	244762-65-0P	244762-66-1P	244762-67-2P	244762-68-3P
	244762-69-4P	244762-70-7P	244762-71-8P	244762-72-9P	244762-73-0P
	244762-74-1P	244762-75-2P	244762-76-3P	244762-77-4P	244762-78-5P
	244762-79-6P	244762-80-9P	244762-81-0P	244762-82-1P	244762-83-2P
	244762-84-3P	244762-85-4P	244762-86-5P	244762-87-6P	244762-88-7P
	244762-89-8P	244762-90-1P	244762-91-2P	244762-92-3P	244762-93-4P
	244762-94-5P	244762-95-6P	244762-96-7P	244762-97-8P	244762-98-9P

244762-99-0P 244763-00-6P **244763-01-7P 244763-02-8P**  
 244763-03-9P 244763-04-0P 244763-05-1P 244763-06-2P 244763-07-3P  
 244763-08-4P 244763-09-5P 244763-10-8P 244763-11-9P 244763-12-0P  
 244763-13-1P 244763-14-2P 244763-15-3P 244763-16-4P 244763-17-5P  
 244763-18-6P 244763-19-7P 244763-20-0P 244763-21-1P 244763-22-2P  
 244763-23-3P 244763-24-4P 244763-25-5P 244763-26-6P 244763-27-7P  
 244763-28-8P 244763-29-9P 244763-30-2P 244763-32-4P 244763-33-5P  
 244763-34-6P 244763-35-7P 244763-36-8P 244763-37-9P 244763-38-0P  
 244763-39-1P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of aralkyl morpholinocyclohexyl ethers and analogs as antiarrhythmic agents)

IT 93-20-9, 2-(2-Naphthoxy)ethanol 110-91-8, Morpholine, reactions  
 111-95-5 117-34-0, Diphenylacetic acid 123-75-1, Pyrrolidine,  
 reactions 286-20-4, Cyclohexene oxide 501-53-1, Benzyl chloroformate  
 504-78-9, Thiazolidine 773-99-9, 1-Naphthaleneethanol 1074-16-4,  
 2-Bromophenethyl alcohol 1124-63-6, 3-Cyclohexyl-1-propanol 1485-07-0,  
 2-Naphthaleneethanol 2799-21-5, (R)-3-Pyrrolidinol 3038-48-0,  
 2-Trifluoromethylphenylacetic acid 3133-87-7, Benzo[b]thiophene-3-  
 ethanol 3929-47-3, 3-(3,4-Dimethoxyphenyl)-1-propanol 4654-39-1,  
 4-Bromophenethyl alcohol 5807-30-7, 3,4-Dichlorophenylacetic acid  
 6575-24-2, 2,6-Dichlorophenylacetic acid 7417-21-2, 3,4-  
 Dimethoxyphenethyl alcohol 13889-98-0, 1-Acetylpiperazine 20443-98-5,  
 2,6-Dichlorobenzyl bromide 28229-69-8, 3-Bromobenzeneethanol  
 34743-88-9, 2-(4-Bromophenoxy)ethanol 227809-74-7, Benzo[b]thiophene-4-  
 ethanol

PL: RCT (Reactant); RACT (Reactant or reagent)

(prepn. of aralkyl morpholinocyclohexyl ethers and analogs as antiarrhythmic agents)

IT 176-33-0P, 1,4-Dioxo-7-azaspiro[4.4]nonane 1883-32-5P 14909-79-6P  
 14909-81-0P 14909-84-3P 30595-79-0P 34094-21-8P 35364-79-5P  
 99176-18-8P 100858-33-1P 130312-02-6P 130993-58-7P 139524-57-5P  
 169191-80-4P 244763-40-4P 244763-41-5P 244763-42-6P 244763-43-7P  
 244763-44-8P 244763-45-9P 244763-46-0P 244763-47-1P 244763-48-2P  
 244763-49-3P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(prepn. of aralkyl morpholinocyclohexyl ethers and analogs as antiarrhythmic agents)

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 RE

- (1) Univ British Columbia; WO 9319056 A 1993 CAPLUS
- (2) Univ British Columbia; WO 9508544 A 1995 CAPLUS

L4 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2003 ACS

AN 1997:400459 CAPLUS

DN 127:108837

TI Preparation of 2-heterocyclylcyclohexyl esters as antiarrhythmics.

IN MacLeod, Bernard A.; Walker, Michael J. A.; Wall, Richard A.

PA University of British Columbia, Can.

SO U.S., 25 pp., Cont.-in-part of U.S. Ser. No. 126,575, abandoned.

CODEN: USXXAM

DT Patent

LA English

IC ICM C07D211-22

ICS C07D295-096; A61K031-445; A61K031-535

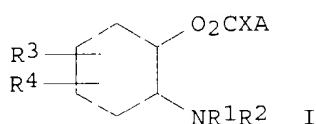
NCL 514212000

09913373

CC 27-9 (Heterocyclic Compounds (One Hetero Atom))  
Section cross-reference(s): 1, 28

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5637583	A	19970610	US 1994-313691	19940927
	CA 2172513	AA	19950330	CA 1994-2172513	19940923
	ES 2170102	T3	20020801	ES 1994-926755	19940923
	US 5885984	A	19990323	US 1997-807728	19970227
	US 6174879	B1	20010116	US 1999-271087	19990317
PRAI	US 1993-126575	B2	19930924		
	US 1994-313691	A3	19940927		
	US 1997-807728	A3	19970227		
OS	MARPAT 127:108837				
GI					



AB Title compds. [I; X = bond, (CH<sub>2</sub>)<sub>n</sub>Y (n = 1, 2, 3; Y = bond, O, S), CH(R<sub>12</sub>)Y (R<sub>12</sub> = alkyl, satd. carbocyclyl, Ph, PhCH<sub>2</sub>), C(R<sub>13</sub>):CH (R<sub>13</sub> = H, alkyl, Ph); R<sub>1</sub>, R<sub>2</sub> = H, alkyl, alkoxyalkyl, aralkyl; R<sub>1</sub>R<sub>2</sub>N = (substituted) (ring-fused) heterocyclyl; R<sub>3</sub>, R<sub>4</sub> = H, OH, alkyl, alkoxy, points of attachment of a spiro 5 or 6-membered heterocyclic ring contg. 1 O or S atom; A = alkyl, carbocyclyl, (substituted) Ph, naphthyl, etc.], were prepd. Thus, benzo[b]thiophene-4-acetic acid was converted to the acid chloride, which reacted with trans-2-(4-morpholinyl)cyclohexanol in CHCl<sub>3</sub> to give trans-2-(4-morpholinyl)cyclohexyl benzo[b]thiophene-4-acetate, isolated as the hydrochloride. The latter at 8 .mu.moles/kg/min in rats gave an arrhythmia score of 0.3, vs 7 for vehicle only.

ST aminocyclohexyl ester prepn antiarrhythmic; heterocyclylcyclohexyl ester prepn antiarrhythmic

IT Antiarrhythmics

(prepn. of 2-heterocyclylcyclohexyl esters as antiarrhythmics)

IT 169191-20-2P 169191-22-4P 169191-23-5P 169191-24-6P 169191-25-7P  
169191-26-8P 169191-27-9P **169191-28-0P** 169191-29-1P  
169191-30-4P 169191-31-5P 169191-32-6P 169191-33-7P 169191-34-8P  
169191-35-9P 169191-37-1P 169191-49-5P 169191-50-8P 169191-52-0P  
169191-53-1P 169191-54-2P 169191-55-3P 169191-56-4P  
**169191-57-5P** 169191-58-6P 169191-59-7P 169191-60-0P  
169191-61-1P 169191-62-2P 169191-63-3P 169191-64-4P 169191-65-5P  
169191-67-7P 169191-69-9P 169191-71-3P 169191-74-6P 169191-76-8P  
169191-77-9P 192446-64-3P 192446-65-4P 192446-66-5P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of 2-heterocyclylcyclohexyl esters as antiarrhythmics)

IT 74-88-4, Methyl iodide, reactions 86-55-5, 1-Naphthoic acid 86-87-3, 1-Naphthylacetic acid 103-82-2, Phenylacetic acid, reactions 104-03-0, 4-Nitrophenylacetic acid 109-01-3, N-Methylpiperazine 110-91-8, Morpholine, reactions 111-49-9 111-95-5 123-75-1, Pyrrolidine, reactions 283-24-9, 3-Azabicyclo[3.2.2]nonane 286-20-4, Cyclohexene oxide 286-28-2, Cyclohexene sulfide 581-96-4, 2-Naphthylacetic acid 588-22-7, 3,4-Dichlorophenoxyacetic acid 628-41-1, 1,4-Cyclohexadiene

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1131-09-5, Benzo[b]thiophene-3-acetic acid 1202-39-7,  
3,4-Dichlorocinnamic acid 1878-68-8, 4-Bromophenylacetic acid  
2635-75-8, Benzo[b]thiophene-4-acetic acid 5292-21-7, Cyclohexylacetic  
acid

RL: PCT (Reactant); RACT (Reactant or reagent)

(prepn. of 2-heterocyclylcyclohexyl esters as antiarrhythmics)

IT 14909-79-6P 14909-81-0P 65173-64-0P 100696-05-7P 125210-15-3P  
152885-54-6P 169191-78-0P 169191-79-1P 169191-80-4P 169191-81-5P

RL: PCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
(Reactant or reagent)

(prepn. of 2-heterocyclylcyclohexyl esters as antiarrhythmics)

L4 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2003 ACS

AN 1995:867587 CAPLUS

DN 123:286082

TI Preparation of heterocyclohexyl esters as antiarrhythmics

IN MacLeod, Bernard A.; Walker, Michael J. A.; Wall, Richard A.

PA University of British Columbia, Can.

SO PCT Int. Appl., 91 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM C07D295-08

ICS C07D223-14; C07D333-56; C07D333-54; C07D307-80; C07C219-24;

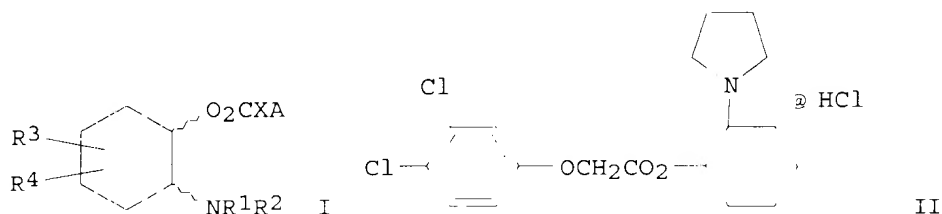
C07C233-30; C07D307-94; A61K031-215

CC 28-17 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9508544	A1	19950330	WO 1994-CA513	19940923
	W: AU, BR, CA, CN, CZ, FI, HU, JP, KR, NO, NZ, PL, RU, UA				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	CA 2172513	AA	19950330	CA 1994-2172513	19940923
	AU 9476502	A1	19950410	AU 1994-76502	19940923
	EP 720605	A1	19960710	EP 1994-926755	19940923
	EP 720605	B1	20011219		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	AT 211135	E	20020115	AT 1994-926755	19940923
	ES 2170102	T3	20020801	ES 1994-926755	19940923
PRAI	US 1993-126575	A	19930924		
	WO 1994-CA513	W	19940923		
OS	MARPAT 123:286082				
GI					



AB Title compds. I ( X = bond, (CH2)nY, CH(R12)Y, CR13:CH wherein n = 1-3, Y  
= bond, O, S, R12 = C1-6 alkyl, C3-6 carbocyclyl, Ph, PhCH2, R13 = H, C1-6

alkyl, Ph; R1, R2 =H, C3-8 alkyl, C3-8 alkoxyalkyl, C7-12 aralkyl; R1R2 = (substituted)heterocyclyl; R3, R4 = H, HO, C1-6 alkyl, C1-6 alkoxy, etc.; A = C5-12 alkyl, (substituted)Ph, etc.), a solvate or salt thereof, are prepd. I are also useful as ion e.g., Na channel blockers. Pyrrolidine, cyclohexene oxide and water were reacted to give (+-)-trans-[2(1-pyrrolidinyl)]cyclohexanol to which was added 3,4-dichlorophenoxyacetyl chloride to give the title compd. (+-)-trans-II. Antiarrhythmic and Na channel blocking activity were demonstrated.

ST heterocyclyl ester prepn antiarrhythmic; ion channel blocker heterocyclyl ester prepn; pyrrolidinylcyclohexyl dichlorophenoxyacetate prepn antiarrhythmic; piperazinylcyclohexyl naphthylacetate prepn antiarrhythmic

IT Antiarrhythmics

Ion channel blockers

(prepn. of heterocyclohexyl esters as antiarrhythmics)

IT 109-01-3, 1-Methylpiperazine

RL: RCT (Reactant); RACT (Reactant or reagent)

(lprepn. of heterocyclohexyl esters as antiarrhythmics)

IT	169191-20-2P	169191-21-3P	169191-22-4P	169191-23-5P	169191-24-6P
	169191-25-7P	169191-26-8P	169191-27-9P	<b>169191-28-0P</b>	
	169191-29-1P	169191-30-4P	169191-31-5P	169191-32-6P	169191-33-7P
	169191-34-8P	169191-35-9P	169191-36-0P	169191-37-1P	169191-38-2P
	169191-39-3P	169191-40-6P	169191-41-7P	169191-42-8P	169191-43-9P
	169191-44-0P	169191-45-1P	169191-46-2P	169191-47-3P	169191-48-4P
	169191-49-5P	169191-50-8P	169191-51-9P	169191-52-0P	169191-53-1P
	169191-54-2P	169191-55-3P	169191-56-4P	<b>169191-57-5P</b>	
	169191-58-6P	169191-59-7P	169191-60-0P	169191-61-1P	169191-62-2P
	169191-63-3P	169191-64-4P	169191-65-5P	169191-66-6P	169191-67-7P
	169191-68-8P	169191-69-9P	169191-70-2P	169191-71-3P	169191-72-4P
	169191-73-5P	169191-74-6P	169191 75 7P	169191-76-8P	169191-77-9P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of heterocyclohexyl esters as antiarrhythmics)

IT 86-87-3, 1-Naphthylacetic acid 103-80-0, Phenylacetyl chloride  
 110-89-4, Piperidine, reactions 110-91-8, Morpholine, reactions  
 111-49-9 111-95-5 123-75-1, Pyrrolidine, reactions 283-24-9,  
 3-Azabicyclo[3.2.2]nonane 286-20-4, Cyclohexene oxide 286-28-2,  
 Cyclohexene sulfide 586-75-4, 4-Bromobenzoyl chloride 628-41-1,  
 1,4-Cyclohexadiene 879-18-5, 1-Naphthoyl chloride 1871-76-7,  
 Diphenylacetyl chloride 2007-12-7, 1-Naphthoxyacetyl chloride  
 2251-65-2, 3-(Trifluoromethyl)benzoyl chloride 5078-73-9,  
 2-(1-Naphthyl)propionyl chloride 7031-27-8, Thiophenoxyacetyl chloride  
 10313-60-7, (3,4-Dimethoxyphenyl)acetyl chloride 20143-45-7,  
 3,4-Dichlorophenoxyacetyl chloride 20850-12-8, 3,4-Dichlorocinnamyl  
 chloride 23860-35-7, Cyclohexylacetyl chloride 24168-51-2,  
 9-Fluoreneacetyl chloride 37859-24-8, 4-Bromophenylacetyl chloride  
 37859-25-9, 2-Naphthylacetyl chloride 50434-36-1, 4-Nitrophenylacetyl  
 chloride 86790-43-4, Benzofuran-2-acetyl chloride 100068-20-0,  
 3-Thianaphtheneacetyl chloride 129392-95-6, 1-Acenaphthenecarbonyl  
 chloride

RL: RCT (Reactant); RACT (Reactant or reagent)

(prepn. of heterocyclohexyl esters as antiarrhythmics)

IT 3117-51-9P, 2-(1-Naphthyl)propionic acid 7581-94-4P,  
 trans-2-(1-Piperidinyl)cyclohexanol 14909-79-6P, trans-2-(4-Morpholinyl)cyclohexanol 14909-81-0P, trans-2-(1-Pyrrolidinyl)cyclohexanol 65173-64-0P, cis-4,5-Cyclohexenediol 100696-05-7P, trans-2-(4-Methyl-1-piperazinyl)cyclohexanol 125210-15-3P, cis-4,5-Dimethoxycyclohexene 152885-54-6P, (1.alpha.,2.beta.,4.beta.,5.b eta.)-4,5-Dimethoxy-2-(1-pyrrolidinyl)cyclohexanol 155528-15-7P,

trans-2-(Diisopropylamino)cyclohexanol 169191-78-0P,  
 trans-2-[N-(3-Azabicyclo[3.2.2]nonyl)]cyclohexanol 169191-79-1P,  
 trans-2-(1-Hexahydroazepinyl)cyclohexanol 169191-80-4P,  
 trans-2-[Bis(2-methoxyethyl)amino]cyclohexanol 169191-81-5P,  
 trans-2-(4-Morpholinyl)cyclohexanethiol 169191-82-6P,  
 trans-2-[Bis(2-methoxyethyl)amino]cyclohexanethiol 169191-83-7P,  
 7-(1-Pyrrolidinyl)-1-oxaspiro[4.5]decan-8-ol  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
 (Reactant or reagent)  
 (prepn. of heterocyclohexyl esters as antiarrhythmics)

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L4 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:591832 CAPLUS

DOCUMENT NUMBER: 136:63572

TITLE: pH-dependent blocking actions of three novel  
 antiarrhythmic compounds on K<sup>+</sup> and Na<sup>+</sup> currents in rat  
 ventricular myocytes

AUTHOR(S): Franciosi, S.; McLarnon, J. G.

CORPORATE SOURCE: Department of Pharmacology and Therapeutics,  
 University of British Columbia, Faculty of Medicine,  
 Vancouver, BC, V6T 1Z3, Can.

SOURCE: European Journal of Pharmacology (2001), 425(2),  
 95-107

CODEN: EJPHAZ; ISSN: 0014-2999

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Three novel chem. related compds. were studied for their pH-dependent ion channel blocking actions on the transient outward K<sup>+</sup> current (I<sub>to</sub>) and the Na<sup>+</sup> current (I<sub>Na</sub>) in isolated rat ventricular myocytes. The (.-.-)-trans-naphthylethoxycyclohexylamines, RSD1108, RSD1070 and RSD1067, showed similar potencies in reducing the inactivation time course of I<sub>to</sub> at pH 7.4. However, RSD1108 (pK<sub>a</sub> 6.8) was a more potent blocker of I<sub>to</sub> at pH 6.4 than the other two compds. (pK<sub>a</sub> values near 8.0). The redn. of inactivation times induced by the RSD compds. was consistent with open channel blockade and in consequence an open channel block model was used in order to est. blocking and unblocking rate consts. This anal. showed no apparent correlation between pK<sub>a</sub> and onward blocking rate consts. for the compds. However, the unblocking rate const. for the low pK<sub>a</sub> compd. RSD1108 at acid pH decreased markedly from that found at normal pH. Both RSD1108 and RSD1070 showed an enhanced potency to block I<sub>Na</sub> at acid pH relative to pH 7.4. However, RSD1108 showed significantly less inhibition of I<sub>Na</sub> at both pH values compared to RSD1070 and RSD1067. Differences in channel block were also evident between RSD1070 and RSD1067, which could be attributed to the difference in naphthyl groups between their chem. structures. The compds. exhibited use- and frequency-dependent blockade of I<sub>Na</sub> with the amt. of use-dependent blockade greater for RSD1108 and RSD1067 than for RSD1070 at acid pH compared to neutral pH. Greater frequency-dependent inhibition was apparent for RSD1108 as compared to RSD1070 and RSD1067 at both pH 7.4 and 6.4. These results point out the importance of the magnitude of pK<sub>a</sub> and chem. structure in ion channel blocking actions of a series of structurally related compds.

IT 244762-60-5, RSD 1067

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PRP (Properties); BIOL (Biological study)

(pH-dependent blocking actions of novel antiarrhythmic compds. on K<sup>+</sup>

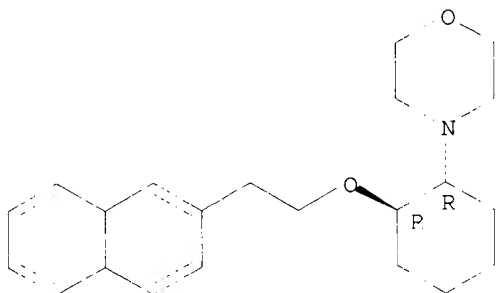
09913373

and Na<sup>+</sup> currents in rat ventricular myocytes)

RN 244762-60-5 CAPLUS

CN Morpholine, 4-[(1R,2R)-2-[2-(2-naphthalenyl)ethoxy]cyclohexyl]-,  
hydrochloride, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



● HCl

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:573767 CAPLUS

DOCUMENT NUMBER: 133:176973

TITLE: Cycloalkyl amine compounds and their use as  
antiarrhythmics and sodium channel blockers

INVENTOR(S): Beatch, Gregory N.; Plouvier, Bertrand M. C.; Walker,  
Michael J. A.; Wall, Richard A.; Zolotoy, Alexander B.

PATENT ASSIGNEE(S): Nortran Pharmaceuticals Inc., Can.

SOURCE: PCT Int. Appl., 59 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

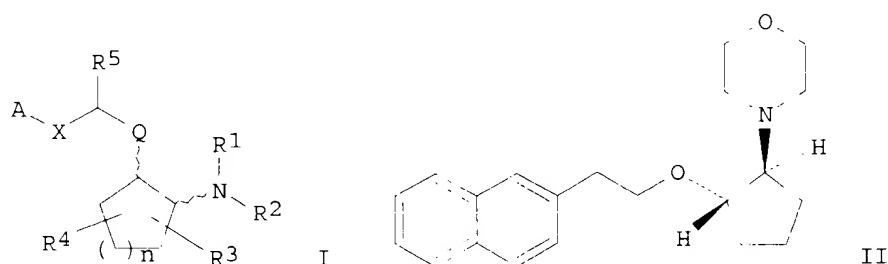
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000047547	A2	20000817	WO 2000-CA117	20000210
WO 2000047547	A3	20001214		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU,  
CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,  
IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,  
MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI,  
SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM,  
AZ, BY, KG, KZ, MD, RU, TJ, TM  
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,  
DK, ES, FI, FP, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,  
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-119887P P 19990212

OTHER SOURCE(S): MARPAT 133:176973

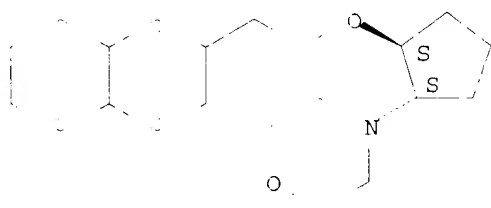
GI



- AB Aminocycloalkyl compds. I are disclosed [wherein  $n = 1, 3, 4$ ;  $Q = O$  or  $OCO$ ;  $X = \text{bond, (un)substituted } CH_2Y, \text{ (un)substituted } CH:CH$ ;  $Y = \text{bond, O, S, alkylene}$ ;  $R_1, R_2 = H, \text{ alkyl, alkoxyalkyl, hydroxyalkyl, aralkyl}$ ; or  $NR_1R_2$  may form a variety of mono- or bicyclic ring systems;  $R_3, R_4 = H, OH, \text{ alkyl, alkoxy}$ ; or  $R_3R_4$  may form a spiro ring with 5 or 6 members and 1 or 2 atoms of O and/or S;  $R_5 = H, \text{ alkyl, aryl, benzyl}$ ;  $A = \text{alkyl, carbocyclyl, or (un)substituted Ph, naphthyl, indenyl, indolyl, acenaphthenyl, or fluorenyl}$ ]. The compds. may be incorporated in compns. and kits. The invention also discloses a wide variety of in vitro and in vivo uses for the compds. and compns., including the treatment of arrhythmia and the prodn. of local analgesia and anesthesia. Two examples were prepd. as HCl salts, and their free bases and their salts and solvates are claimed. For instance, (1R,2R)/(1S,2S)-II.HCl (III) was prepd. by a sequence of: (1) reaction of morpholine with cyclopentene oxide; (2) mesylation of the resulting alc.; (3) etherification of the mesylate with 2-naphthaleneethanol; and (4) acidification with ethereal HCl. In a test for efficacy against cardiac arrhythmias in rats (induced by coronary artery occlusion), III had an ED<sub>50</sub> of 1.5  $\mu\text{M/kg/min i.v.}$
- IT **288394-73-0P**, (1R,2R)/(1S,2S)-2-(4-Morpholinyl)-1-(2-naphthaleneethoxy)cyclopentane monohydrochloride **288394-75-2P**, (1R,2R)/(1S,2S)-2-(4-Morpholinyl)-1-(2-naphthaleneethoxy)cyclopentane  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (drug candidate; prepn. of cycloalkylamine derivs. as antiarrhythmics and sodium channel blockers)
- RN 288394-73-0 CAPLUS
- CN Morpholine, 4-[(1R,2R)-2-[2-(2-naphthalenyl)ethoxy]cyclopentyl]-, hydrochloride, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

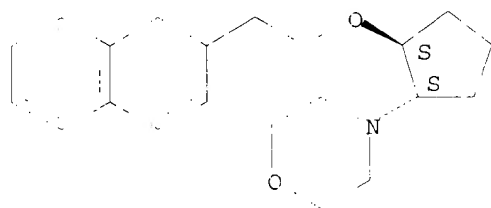
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● HCl

PN 288394-75-2 CAPLUS  
CN Morpholine, 4-[(1R,2R)-2-[2-(2-naphthalenyl)ethoxy]cyclopentyl]-, rel-  
(9CI) (CA INDEX NAME)

Relative stereochemistry.



L4 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2003 ACS  
ACCESSION NUMBER: 1999:640819 CAPLUS  
DOCUMENT NUMBER: 131:257571  
TITLE: Preparation of aralkyl morpholinocyclohexyl ethers and  
analogues as antiarrhythmic agents  
INVENTOR(S): Bain, Allen I.; Beatch, Gregory N.; Longley, Cindy J.;  
Plouvier, Bertrand M. C.; Sheng, Tao; Walker, Michael  
J. A.; Wall, Richard A.; Yong, Sandro L.; Zhu, Jiqun;  
Zolotoy, Alexander B.  
PATENT ASSIGNEE(S): Nortran Pharmaceuticals Inc., Can.  
SOURCE: PCT Int. Appl., 141 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9950225	A1	19991007	WO 1999-CA280	19990401
W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
PW:	GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,			

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CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

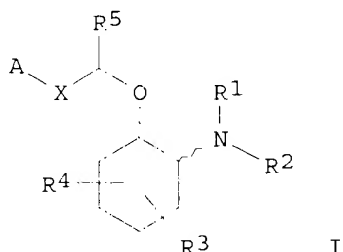
CA 2326777	AA	19991007	CA 1999-2326777	19990401
AU 9930215	A1	19991018	AU 1999-30215	19990401
AU 751772	B2	20020829		
EP 1087934	A1	20010404	EP 1999-911550	19990401

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
IE, LT, LV, FI

BR 9909282	A	20011016	BR 1999-9282	19990401
EE 200000583	A	20020215	EE 2000-200000583	19990401
JP 2002509908	T2	20020402	JP 2000-541135	19990401
NO 2000004897	A	20001113	NO 2000-4897	20000929

PRIORITY APPLN. INFO.: US 1998-80347P P 19980401  
US 1999-118954P P 19990205  
WO 1999-CA280 W 19990401

OTHER SOURCE(S): MARPAT 131:257571  
GI



AB R3CHR5OZ1NR1R2 [R = (cyclo)alkyl, (un)substituted Ph, -naphthyl, etc.; R1,R2 = H, (ar)alkyl, alkoxyalkyl, hydroxyalkyl; NR1R2 = heterocyclyl; R5 = H, alkyl, CH2Ph, aryl; Z = bond, (un)substituted alkylene, -CH2O, -CH:CH, etc.; Z1 = (un)substituted 1,2-cyclohexylene] were prepd. as cardiac Na channel blockers. Thus, cyclohexene oxide was aminated by morpholine and the O-mesylated product etherified by 2-naphthaleneethanol to give title compd. trans-I.

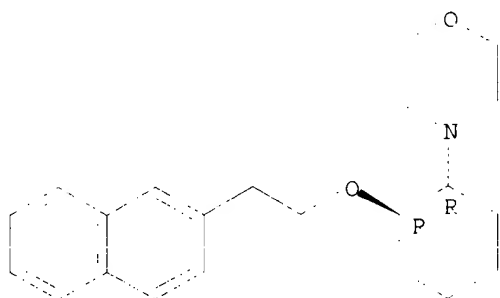
IT **244762-60-5P 244762-61-6P 244763-01-7P 244763-02-8P**  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(prepn. of aralkyl morpholinocyclohexyl ethers and analogs as antiarrhythmic agents)

RN 244762-60-5 CAPLUS

CN Morpholine, 4-[(1R,2R)-2-[2-(2-naphthalenyl)ethoxy]cyclohexyl]-, hydrochloride, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

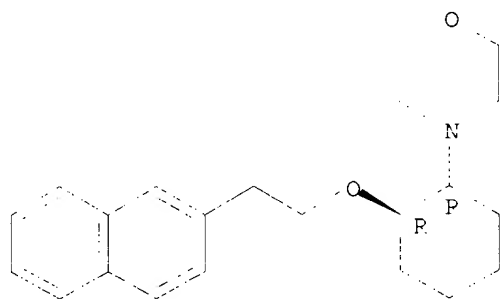
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● HCl

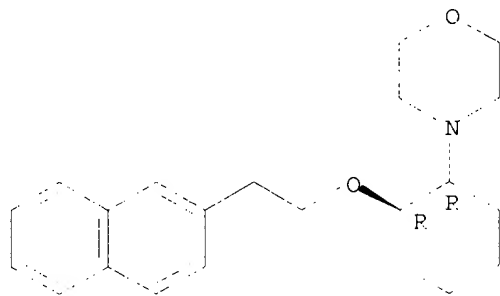
RN 244762-61-6 CAPLUS  
CN Morpholine, 4-[(1R,2R)-2-[2-(2-naphthalenyl)ethoxy]cyclohexyl]-, rel-(9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 244763-01-7 CAPLUS  
CN Morpholine, 4-[(1R,2R)-2-[2-(2-naphthalenyl)ethoxy]cyclohexyl]-, rel-(+)-(9CI) (CA INDEX NAME)

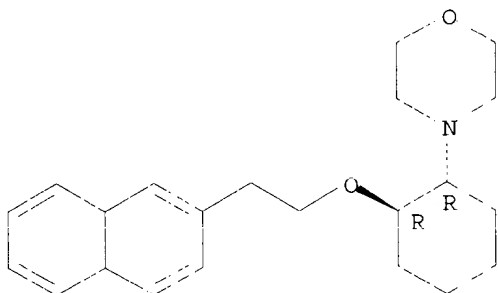
Rotation (+). Absolute stereochemistry unknown.



RN 244763-02-8 CAPLUS  
CN Morpholine, 4-[(1R,2R)-2-[2-(2-naphthalenyl)ethoxy]cyclohexyl]-, rel-(-)-(9CI) (CA INDEX NAME)

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Rotation (-). Absolute stereochemistry unknown.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1997:400459 CAPLUS

DOCUMENT NUMBER: 127:108837

TITLE: Preparation of 2-heterocyclylcyclohexyl esters as antiarrhythmics.

INVENTOR(S): MacLeod, Bernard A.; Walker, Michael J. A.; Wall, Richard A.

PATENT ASSIGNEE(S): University of British Columbia, Can.

SOURCE: U.S., 25 pp., Cont.-in-part of U.S. Ser. No. 126,575, abandoned.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

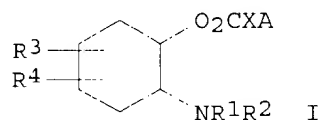
FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5637583	A	19970610	US 1994-313691	19940927
CA 2172513	AA	19950330	CA 1994-2172513	19940923
ES 2170102	T3	20020801	ES 1994-926755	19940923
US 5885984	A	19990323	US 1997-807728	19970227
US 6174879	B1	20010116	US 1999-271087	19990317
PRIORITY APPLN. INFO.:			US 1993-126575	B2 19930924
			US 1994-313691	A3 19940927
			US 1997-807728	A3 19970227

OTHER SOURCE(S): MARPAT 127:108837

GI



AB Title compds. [I; X = bond, (CH<sub>2</sub>)<sub>n</sub>Y (n = 1, 2, 3; Y = bond, O, S), CH(R<sub>12</sub>)Y (R<sub>12</sub> = alkyl, satd. carbocyclyl, Ph, PhCH<sub>2</sub>), C(R<sub>13</sub>):CH (R<sub>13</sub> = H, alkyl, Ph); R<sub>1</sub>, R<sub>2</sub> = H, alkyl, alkoxyalkyl, aralkyl; R<sub>1</sub>R<sub>2</sub>N = (substituted) (ring-fused) heterocyclyl; R<sub>3</sub>, R<sub>4</sub> = H, OH, alkyl, alkoxy, points of

attachment of a spiro 5- or 6-membered heterocyclic ring contg. 1 O or S atom; A = alkyl, carbocyclyl, (substituted) Ph, naphthyl, etc.], were prepd. Thus, benzo[b]thiophene-4-acetic acid was converted to the acid chloride, which reacted with trans-2-(4-morpholinyl)cyclohexanol in  $\text{CHCl}_3$  to give trans-2-(4-morpholinyl)cyclohexyl benzo[b]thiophene-4-acetate, isolated as the hydrochloride. The latter at 8  $\mu\text{moles/kg/min}$  in rats gave an arrhythmia score of 0.3, vs 7 for vehicle only.

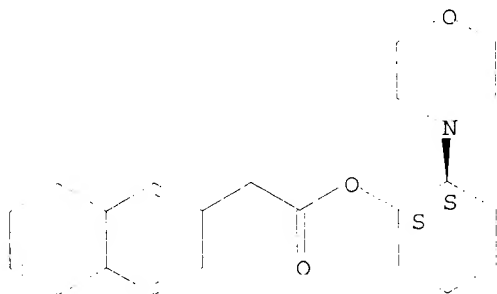
IT 169191-28-0P 169191-57-5P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(prepn. of 2-heterocyclcyclohexyl esters as antiarrhythmics)

RN 169191-28-0 CAPLUS

CN 2-Naphthaleneacetic acid, 2-(4-morpholinyl)cyclohexyl ester, hydrochloride, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.

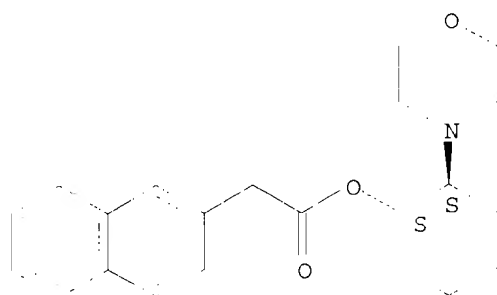


● HCl

RN 169191-57-5 CAPLUS

CN 2-Naphthaleneacetic acid, 2-(4-morpholinyl)cyclohexyl ester, trans- (9CI)  
(CA INDEX NAME)

Relative stereochemistry.



L4 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1995:867587 CAPLUS

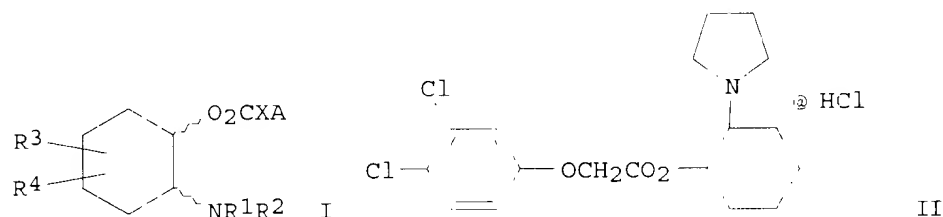
DOCUMENT NUMBER: 123:286082

TITLE: Preparation of heterocyclohexyl esters as

09913373

antiarrhythmics  
 INVENTOR(S): MacLeod, Bernard A.; Walker, Michael J. A.; Wall, Richard A.  
 PATENT ASSIGNEE(S): University of British Columbia, Can.  
 SOURCE: PCT Int. Appl., 91 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 2  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9508544	A1	19950330	WO 1994-CA513	19940923
W: AU, BR, CA, CN, CZ, FI, HU, JP, KR, NO, NZ, PL, RU, UA				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2172513	AA	19950330	CA 1994-2172513	19940923
AU 9476502	A1	19950410	AU 1994-76502	19940923
EP 720605	A1	19960710	EP 1994-926755	19940923
EP 720605	B1	20011219		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
AT 211135	E	20020115	AT 1994-926755	19940923
ES 2170102	T3	20020801	ES 1994-926755	19940923
PRIORITY APPLN. INFO.:			US 1993-126575	A 19930924
			WO 1994-CA513	W 19940923
OTHER SOURCE(S):		MARPAT 123:286082		
GI				

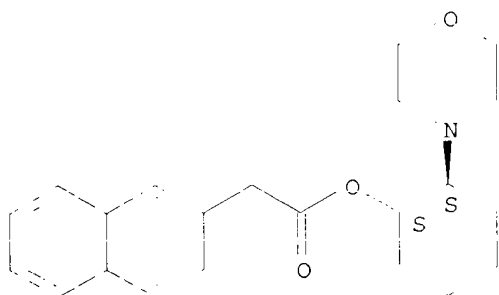


AB Title compds. I (X = bond, (CH<sub>2</sub>)<sub>n</sub>Y, CH(R<sub>12</sub>)Y, CR<sub>13</sub>:CH wherein n = 1-3, Y = bond, O, S, R<sub>12</sub> = C1-6 alkyl, C3-6 carbocyclyl, Ph, PhCH<sub>2</sub>, R<sub>13</sub> = H, C1-6 alkyl, Ph; R<sub>1</sub>, R<sub>2</sub> = H, C3-8 alkyl, C3-8 alkoxyalkyl, C7-12 aralkyl; R<sub>1</sub>R<sub>2</sub> = (substituted)heterocyclyl; R<sub>3</sub>, R<sub>4</sub> = H, HO, C1-6 alkyl, C1-6 alkoxy, etc.; A = C5-12 alkyl, (substituted)Ph, etc.), a solvate or salt thereof, are prepd. I are also useful as ion e.g., Na channel blockers. Pyrrolidine, cyclohexene oxide and water were reacted to give (+-)-trans-[2(1-pyrrolidinyl)]cyclohexanol to which was added 3,4-dichlorophenoxyacetyl chloride to give the title compd. (+-)-trans-II. Antiarrhythmic and Na channel blocking activity were demonstrated.

IT **169191-28-0P 169191-57-5P**  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (prepn. of heterocyclohexyl esters as antiarrhythmics)  
 RN 169191-28-0 CAPLUS  
 CN 2-Naphthaleneacetic acid, 2-(4-morpholinyl)cyclohexyl ester, hydrochloride, trans- (9CI) (CA INDEX NAME)

09913373

Relative stereochemistry.



● HCl

PN 169191 57-5 CAPLUS

CN 2-Naphthaleneacetic acid, 2-(4-morpholinyl)cyclohexyl ester, trans- (9CI)  
(CA INDEX NAME)

Relative stereochemistry.

